Suvorexant Safety and Efficacy

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FDA Preliminary Conclusions

- Suvorexant is effective, but not safe at the higher doses mainly studied
- The lower doses studied have similar efficacy and better safety
- The lowest dose developed, 15 mg, may not be low enough for safe use
- Phase 2 data suggest 10 mg may be effective
- Less than 10 mg not studied, but could be effective

FDA Approach to Insomnia Drugs

Use the lowest dose effective for the patient

- First, and perhaps most important, dosing instruction in new labeling for insomnia drugs
- FDA working to apply to all insomnia drugs approved and in development
- Dosage forms should be available to allow patients to take a safe and effective dose

FDA Approach to Benefit/Risk:

Consider actual, not just ideal use

"Beyond the clinical study…must consider how people actually use…consider cognitive and behavioral factors affecting human judgment and decision-making"*

*Structured approach to benefit-risk assessment in drug regulatory decision-making: Draft PDUFA implementation Plan- Feb 2013

http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf

Key Safety Concerns

- Daytime somnolence can be severe and occur suddenly: *patients drive while impaired*
- Unconscious nighttime activity
- Suicidal ideation

- Other narcolepsy-associated events
  - Sleep paralysis, hypnagogic hallucinations, mild cataplexy

Safety in Patients *not* Studied?

- Enrolled selected, generally healthy patients
- Little data in concomitant diseases, or use with drugs commonly used in actual clinical population
- Adverse effects raise particular concern about safety in some groups not studied
  - Suicidal ideation
    - *23% of all women age 40-59 take antidepressants**
    - Depression and insomnia commonly coexist
  - Nighttime activity
    - Sleepwalking history in 1 to 15% of general population

*http://www.cdc.gov/nchs/data/databriefs/db76.pdf

Not clear how concerned FDA should be about narcolepsy-like events other than somnolence

- Reports like “ Weak knees when laughing” look like mild cataplexy
- Low reported incidence (≈0.1%), but mild cataplexy easily overlooked, and a few reports of ‘weakness’ might also be mild cataplexy
- No cases of more severe cataplexy

Sleep Paralysis and Hallucinations (≈0.3%)

Case examples:

- Around time of sleep onset, inability to move, as if someone holding her down, as well as sensation of an individual in bed with her (20 mg)

- Laid down to sleep and had a feeling as if 'shocked' then felt paralyzed and heard vivid sounds of people coming up the stairs, with a sense of violent intent (30 mg)

Daytime Somnolence

Even though suvorexant increases sleep time, many patients *more* sleepy during day, some *much sleepier* : Dose-related

	Placebo (N=1025)	Low Dose (N=493)	High Dose (N=1291)
Somnolence	3%	7%	11%
'Excessive daytime sleepiness'	0.2%	0.6%	1.1%

- Sponsor defined: beyond potential residual drug effect
- Persistent, recurrent, impairing, may be sudden, involuntary

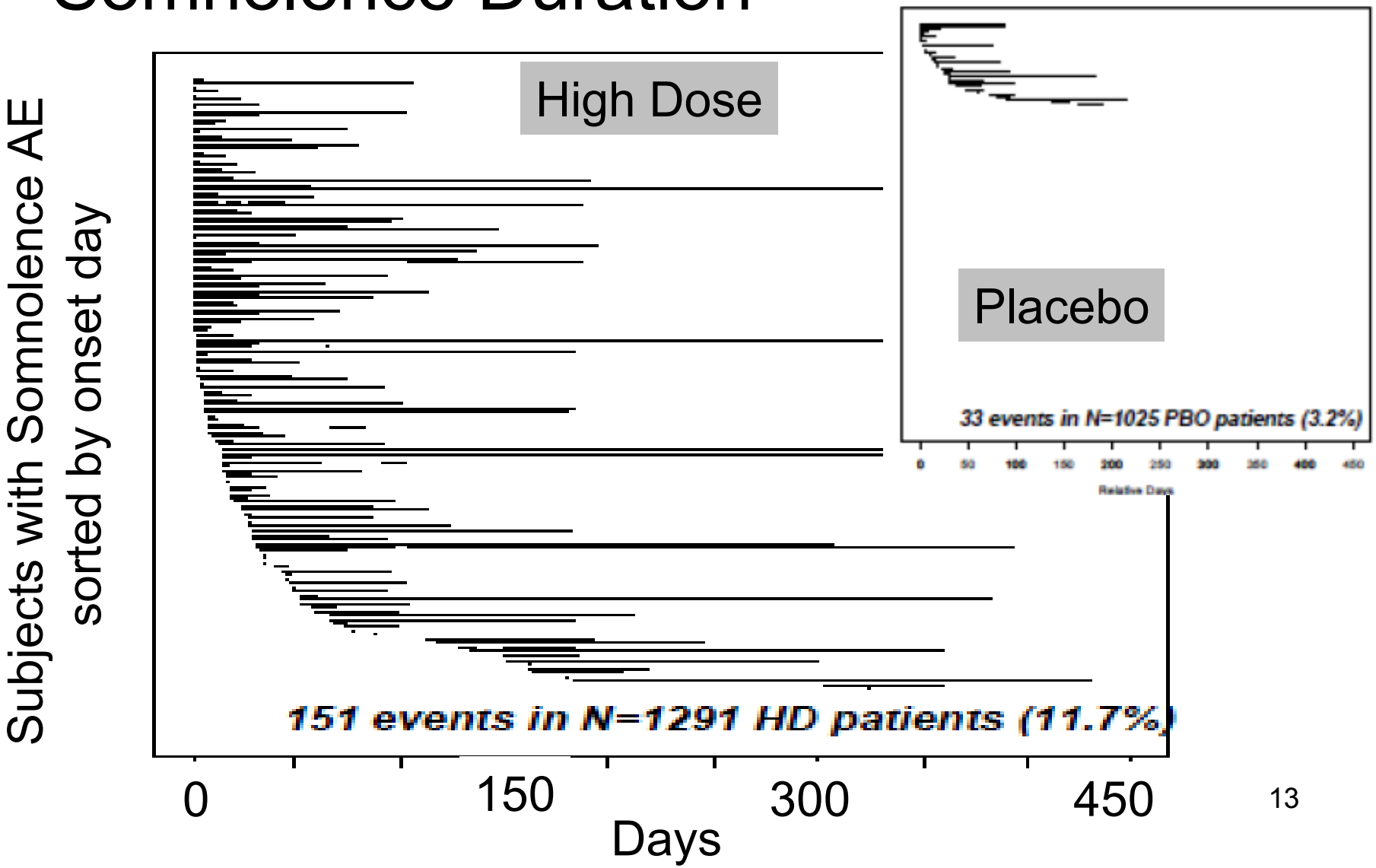
- 59 year old man, 40 mg suvorexant
  - Nodded off at a red light
  - Multiple episodes of nodding off while driving
  - Once *started to veer off road* until wife yelled

(this was the patient with weak knees when laughing)

Excessive Daytime Sleepiness While Driving

- ≈ 0.5% of high dose patients
- Described as:
  - 'Started while driving'
  - 'Difficulty staying awake while driving'
  - 'Need to pull over and rest while driving'
- Placebo - no similar driving events

Somnolence Duration



Patients were unable to avoid driving in the suvorexant studies while seemingly impaired by excessive daytime sleepiness, despite close clinical monitoring and warnings about possible impairment

- *"MK-4305 may make you sleepy"*
- *"Your ability to drive or operate other heavy machinery may be impaired after taking study drug"*

If warnings not effective in study, how will drug be used safely in clinical setting?

Increased FDA understanding that patients are *not* reliably aware of drug impairment…

…and even *if* aware, may still drive

Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality

Joris C. Verster · Thomas Roth

Psychopharmacology 2011

"The general advice that 'patients should listen to their body, and not drive if they feel their driving is impaired' ***should not be relied on*** because patients may not be aware of their driving impairment"

Sponsor:

The higher incidence of drug-related adverse events with suvorexant is not associated with a higher rate of treatment discontinuation compared to placebo

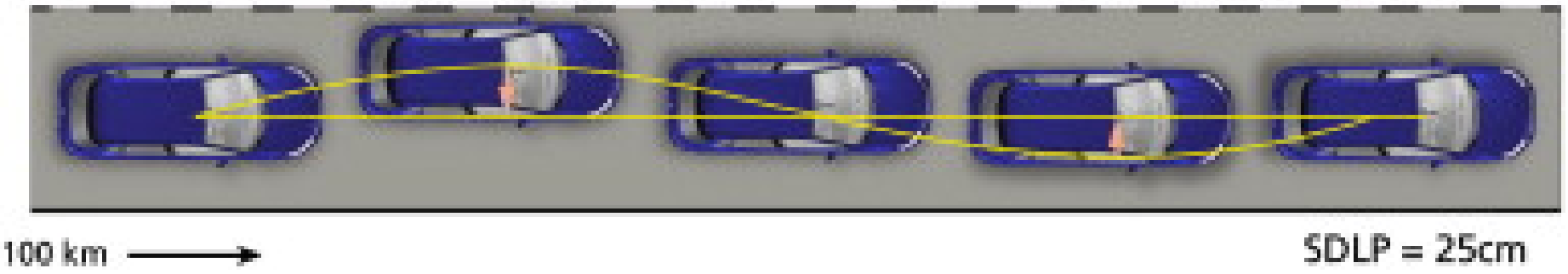
FDA:

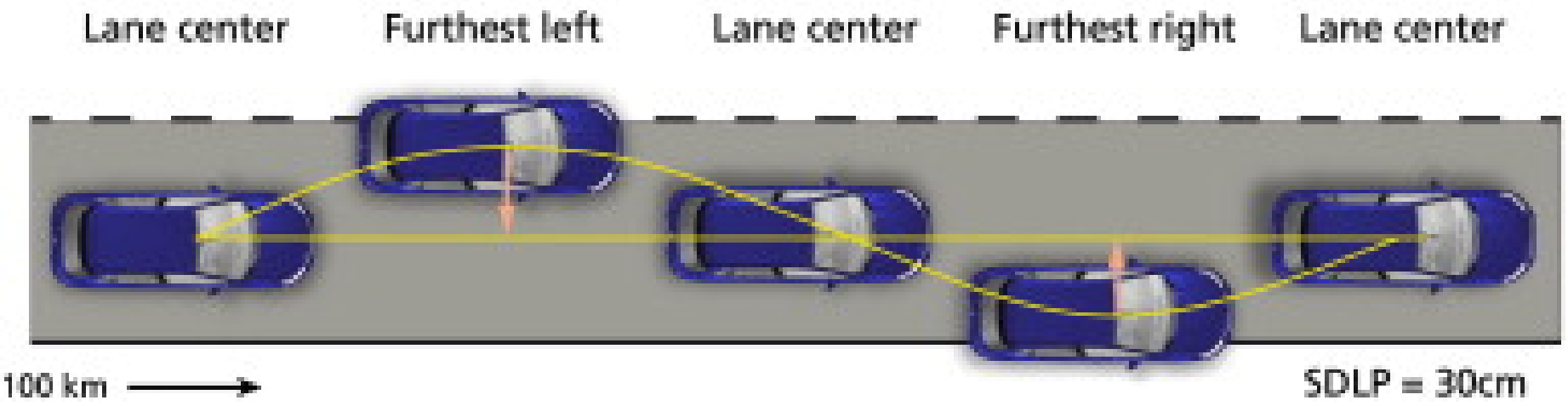
Continued use seems like a safety *problem* for somnolent patients, not evidence of safety

Suvorexant Formal Driving Study

- On-road test of stability of lane position
  - 'Standard Deviation of Lane Position' (SDLP)
- On-face meaningful for safe driving
  - Leaving lane (or roadway) clearly dangerous
- Usual interpretation
  - Meaningful impairment when SDLP worsens by same amount as from alcohol at legal limit in many countries, 0.05%
  - Corresponds to 2.5 cm worsening of SDLP

Standard Deviation of Lateral Position (SDLP)





Verster and Roth 2013, Sleep Medicine Reviews 17:153-159

Driving Study Endpoint

- In hindsight, *falling asleep and leaving road entirely* may be bigger risk than type of impairment causing 'weaving'
- SDLP does *not* measure risk of falling asleep
- SDLP still impaired by suvorexant
  - Sleepiness causes auto crashes because it impairs performance and can lead to inability to resist falling asleep at the wheel*

*http://www.nhtsa.gov/people/injury/drowsy_driving1/drowsy.html

Driving Test Interpretation

- Evaluating average impairment of all patients in study is not sensitive to clinically important impairment in individuals

- Need to ask *how many* patients are affected, and *how severely*

Driving Study Findings

Adult (<65 years)		Elderly (≥ 65 years)	
First night/day	20 mg	First night/day	15 mg
	40 mg		30 mg
After 1 week	20 mg	After 1 week	15 mg
	40 mg		30 mg

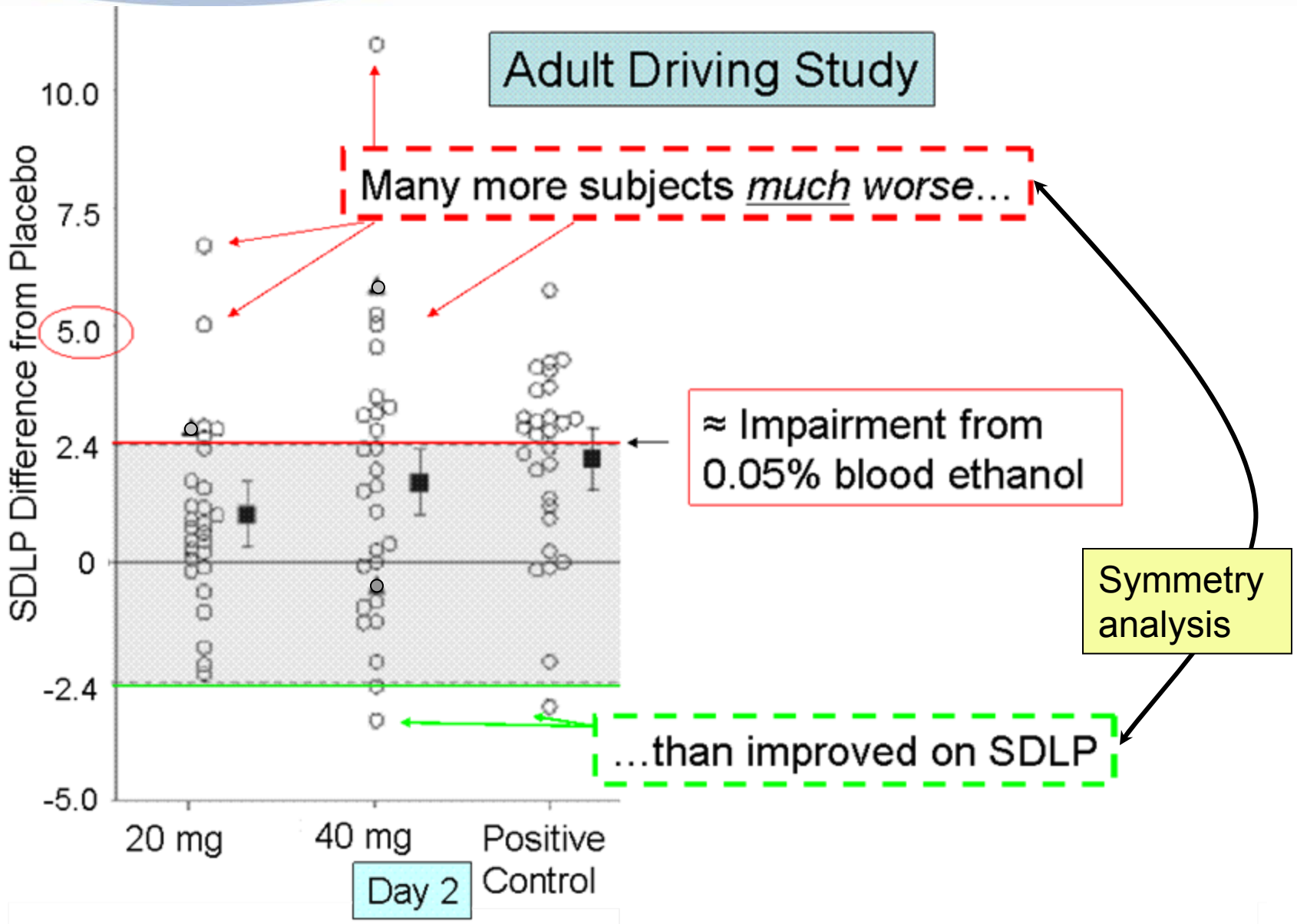
Statistically significant impairment

'Lean' towards significant impairment→ worrisome in small safety study

By 'symmetry analysis': more patients impaired than improved

Approximate Proportion of Impaired Patients

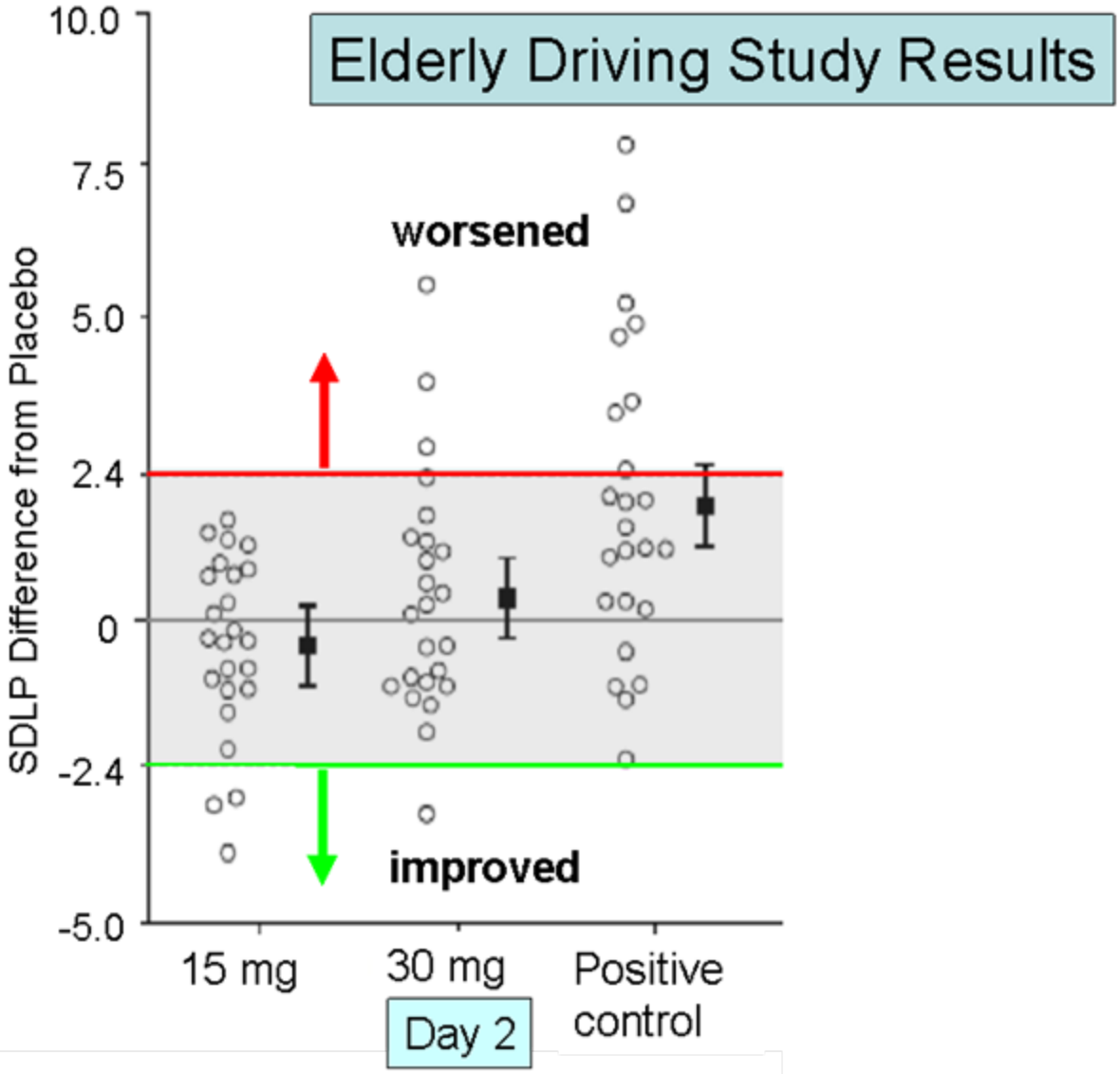
Adult (<65 years)		
First night/day	20 mg:	**≈ 20%** above alcohol cutoff
	40 mg:	**≈ 30%** " "
After 1 week	20 mg:	
	40 mg:	**≈ 20%** " "


Adult Driving Study
Many more subjects much worse…
≈ Impairment from 0.05% blood ethanol
Symmetry analysis
…than improved on SDLP
SDLP Difference from Placebo
10.0
7.5
5.0
2.4
0
-2.4
-5.0
20 mg
40 mg
Positive Control
Day 2

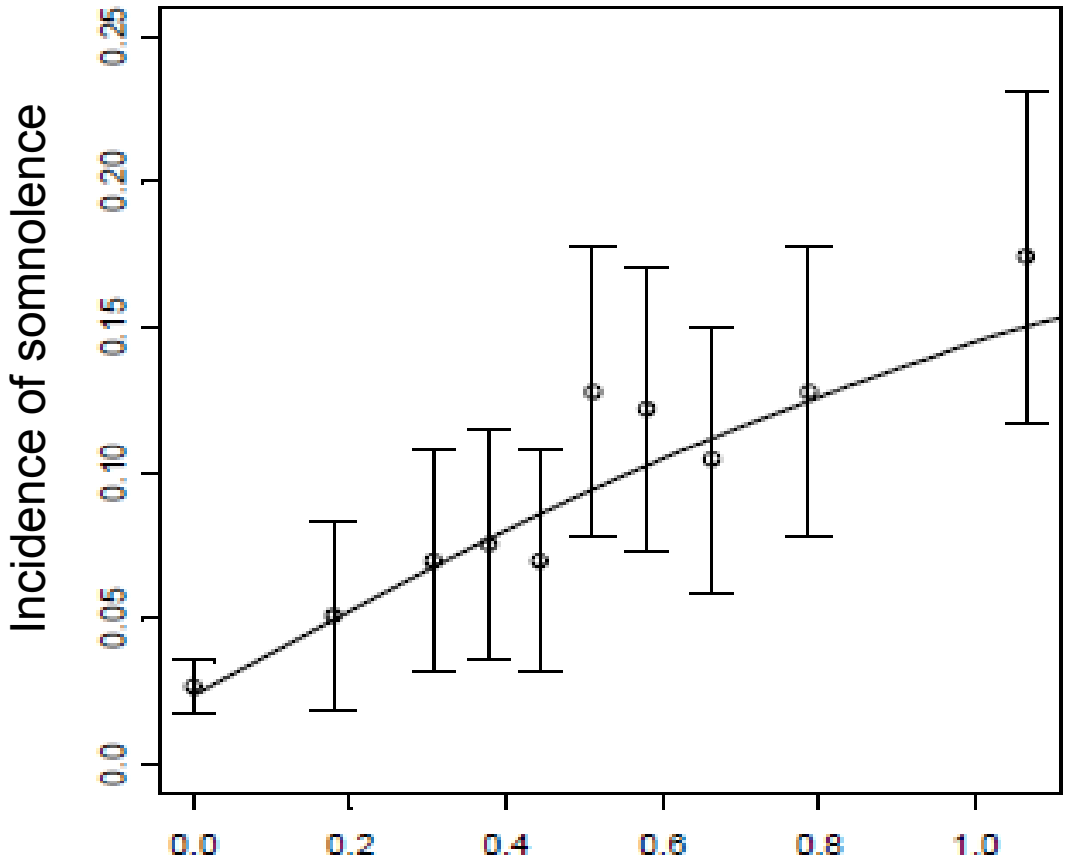
Elderly Driving Study

- 30 mg
  - day 9 very close to statistically positive
  - day 2 trend to impairment

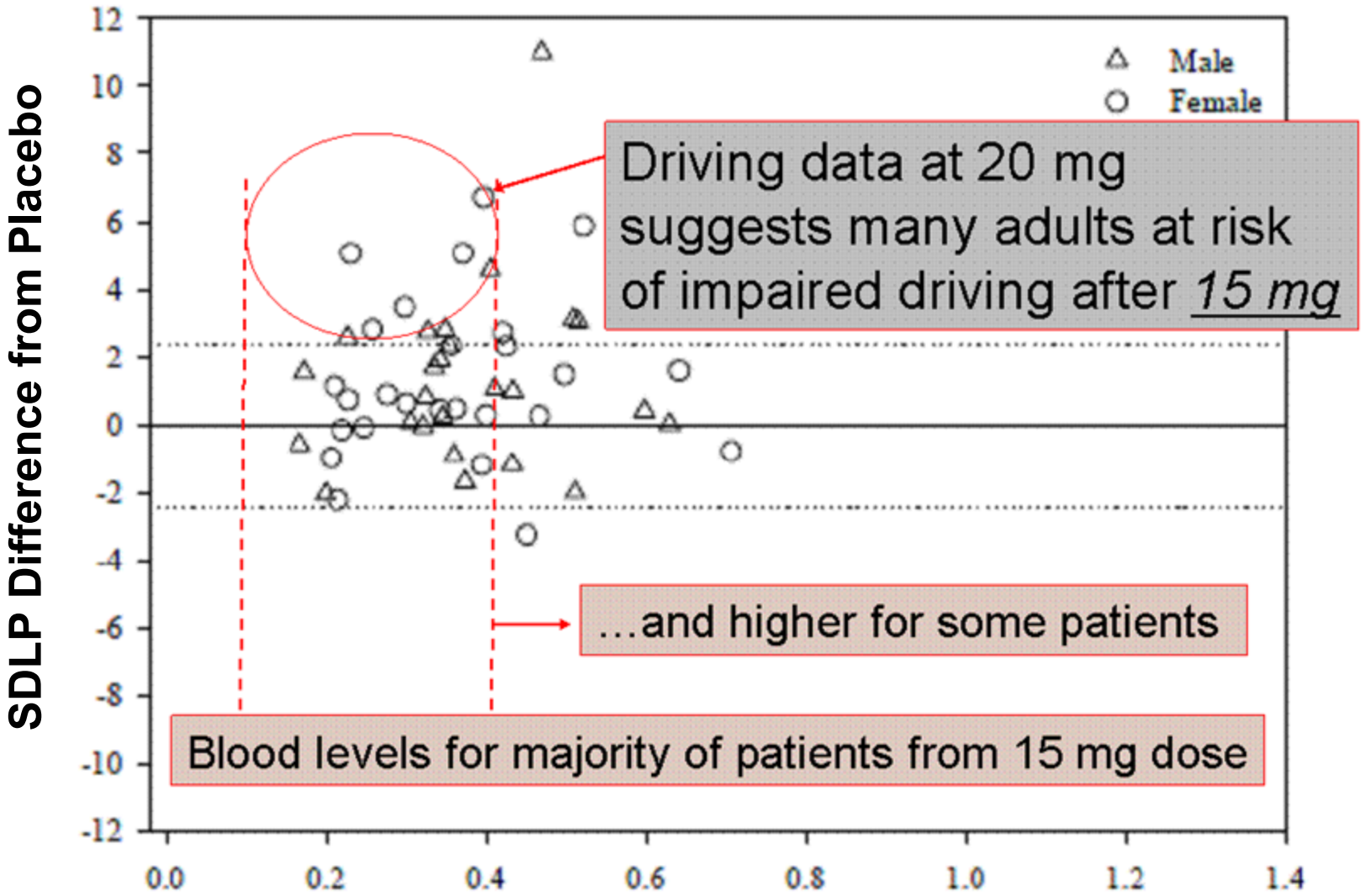
- 15 mg no impairment on SDLP *is* reassuring…
  - But narrow safety margin: 20 mg caused impairment in adults (and 15 mg not studied in adults)
  - Some individual patients, and entire patient subgroups, have *exposure* from the 15 mg dose that is as high, or higher, than exposure from the 20 mg dose


Elderly Driving Study Results
10.0
7.5
5.0
2.4
0
-2.4
-5.0
SDLP Difference from Placebo
worsened
improved
15 mg
30 mg
Positive control
Day 2

Blood *Level*, *Not Just Dose* Correlated to Somnolence



studies 6/28/29/9


SDLP Difference from Placebo
12
10
8
6
4
2
0
-2
-4
-6
-8
-10
-12
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
Male
Female
Driving data at 20 mg suggests many adults at risk of impaired driving after 15 mg
…and higher for some patients
Blood levels for majority of patients from 15 mg dose
Suvorexant Plasma Level, 11 hours after dosing (μM)
Day 2

Unconscious Nighttime Behavior

One Case Resembles REM Sleep Behavior Disorder (RBD)

- Occurs in narcolepsy and other disorders
- Characterized by intense motor or verbal paroxysmal dream-enacting episodes
- Individuals act out dreams, sometimes with serious injury to self and others

65 Year Old Man, 30 mg

- During PSG recording, 2.5 hours after dosing
- Talking in sleep, sat up in bed, went back to sleep
- *Lunged out of bed, and hit his head and face against a wall*

- Sleep walking event after 2 weeks off drug
- Past history of sleep talking, not sleep walking

Concerning to see this type of event in relatively small number of exposed patients

One Case Sleep Walking

- 58 year old women, 40 mg
  - Sleep paralysis
  - Hypnagogic hallucination
  - Several hours later, found herself standing at the window without knowing how she got there

Suicidal Ideation

- Suicidal ideation assessed prospectively with questionnaire
  - Placebo: 0.1% 1 patient
  - Low dose: 0.2% 1 patient
  - High dose 0.7% 9 patients

- Ideation generally ‘mild’, but still thought to indicate increased risk of suicide
- Patients had prior history and/or ongoing psychosocial stress…
- Still consistent with drug-related adverse effect in patients with baseline risk factors

Efficacy

Efficacy Endpoints

- FDA requires both objective and subjective endpoints for various diseases

Objective: show change *occurred*

Subjective: marker suggesting *clinically meaningful*

Subjective Sleep Time

- Known (and shown in suvorexant studies) to be inaccurate; even less accurate *because* of some drugs, potentially including suvorexant
- Sleep might be misperceived as longer due to non-beneficial or even *adverse* drug effect
- Potentially meaningful, but interpret with caution

Effectiveness of 10 mg

- *By pre-specified analysis, 10 mg effective for sleep maintenance in crossover study 006 at night 1 and week 4*

- Study 006 confounded by carryover effect
  - Period 1 improvement in latency to persistent sleep did not diminish in period 2, even though patients on placebo

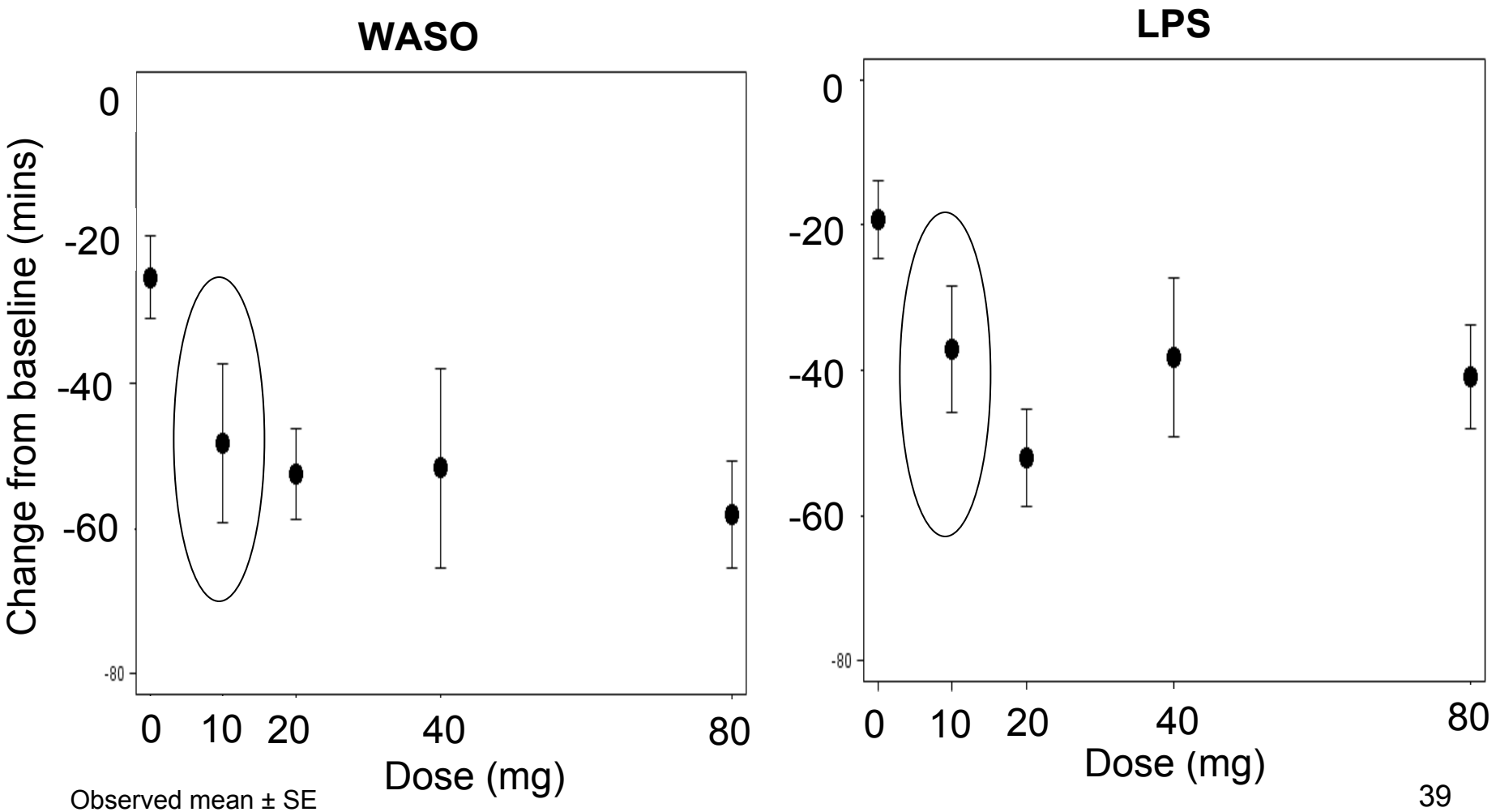
Effectiveness of 10 mg

- FDA analyzed sleep latency for *period 1*
  - by reasonable analyses, evidence of efficacy for 10 mg

Percent decrease in latency to persistent sleep

	Night 1		Week 4	
10 mg	**49%**	**p = 0.02***	**58%**	**p = 0.02***
20 mg	51%		67%	
40 mg	68%		54%	
80 mg	54%		58%	

*nominal p-values



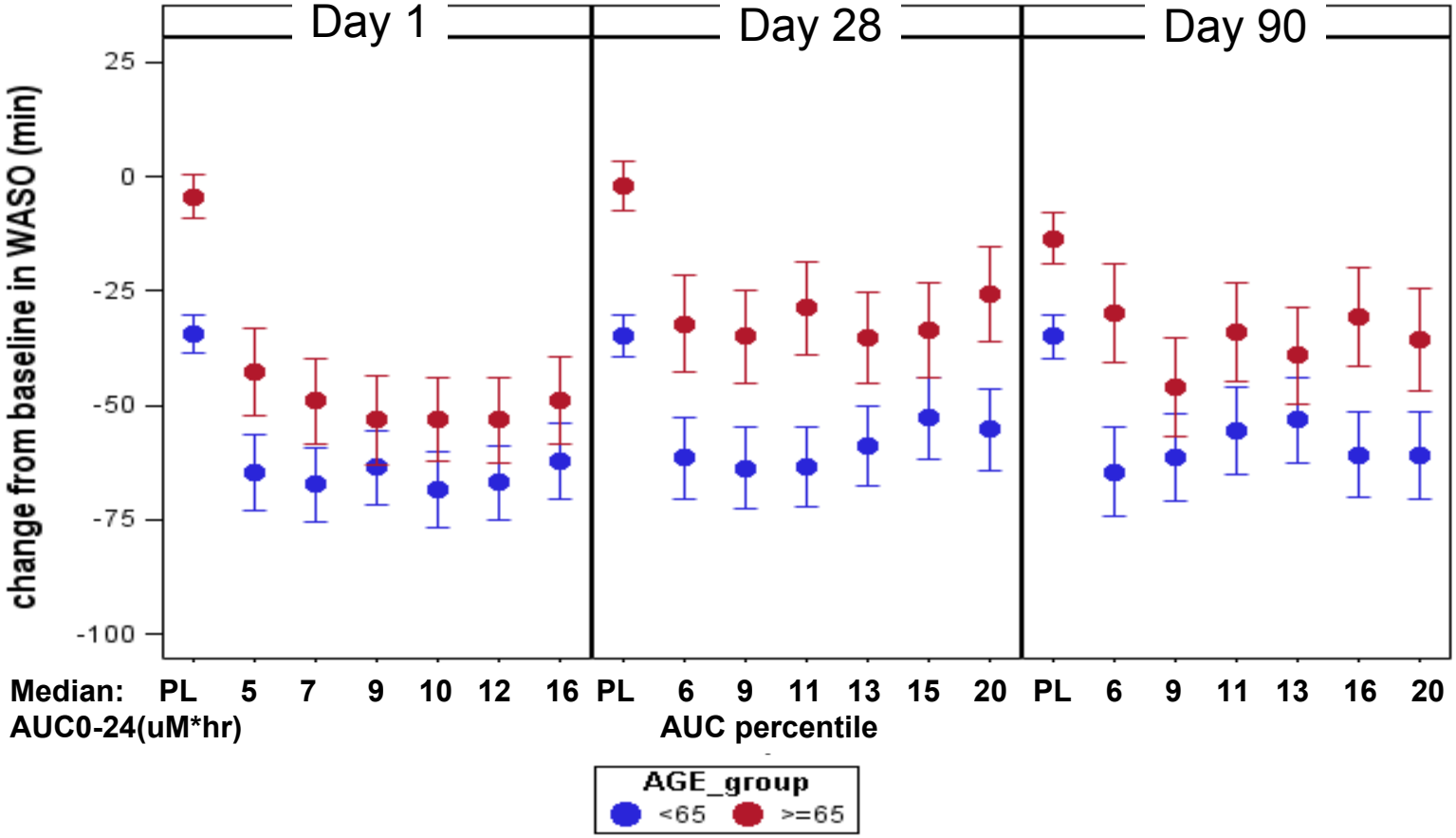
Observed mean ± SE

study 006, 1st period, day 28 'N' ≈ 30 each dose group

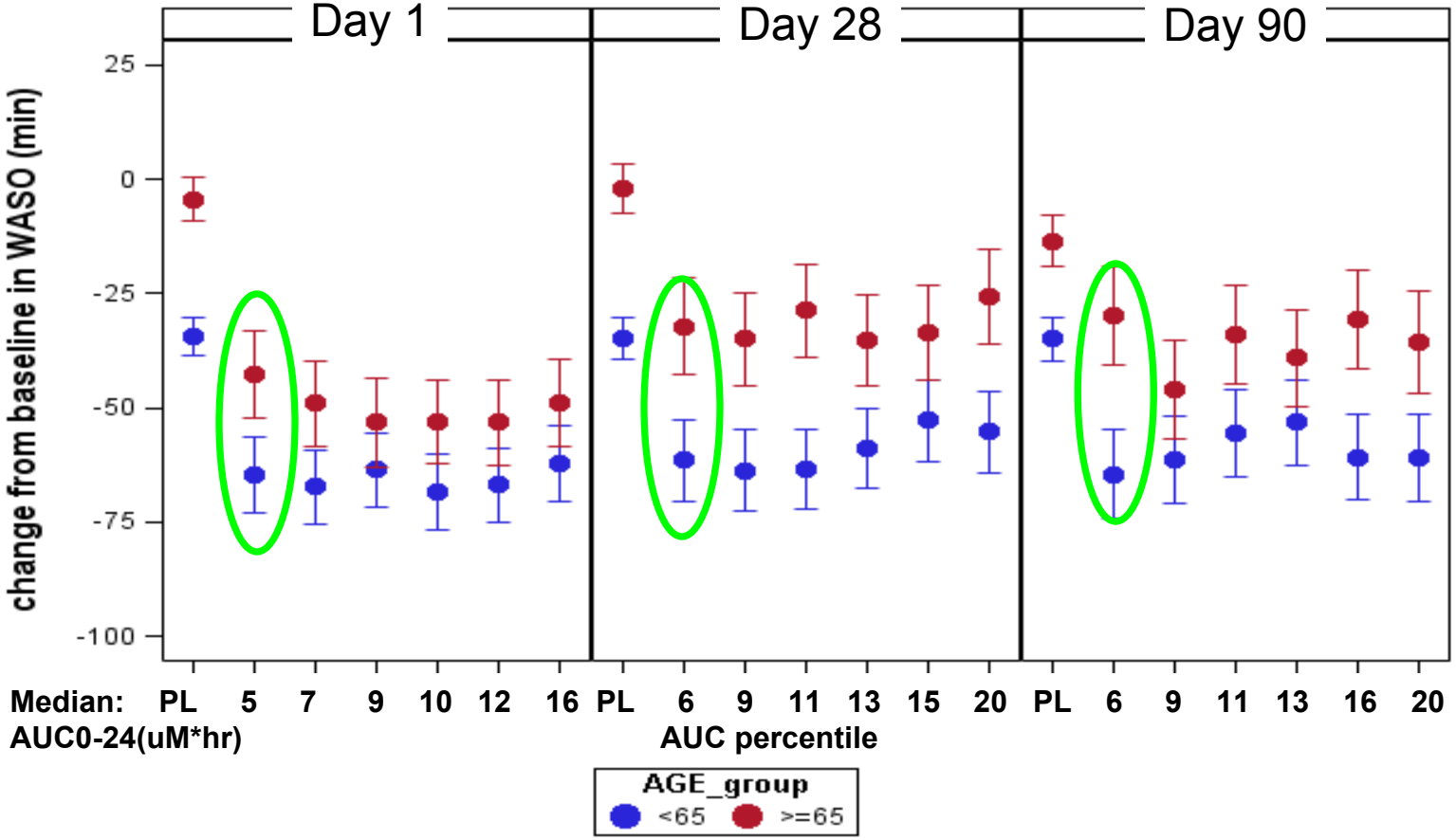
Less Than 10 mg Might Be Effective

- Neither dose-response nor exposure-response analysis of phase 3 trials showed clear diminishment of efficacy at lower exposures, for objective sleep onset or sleep maintenance

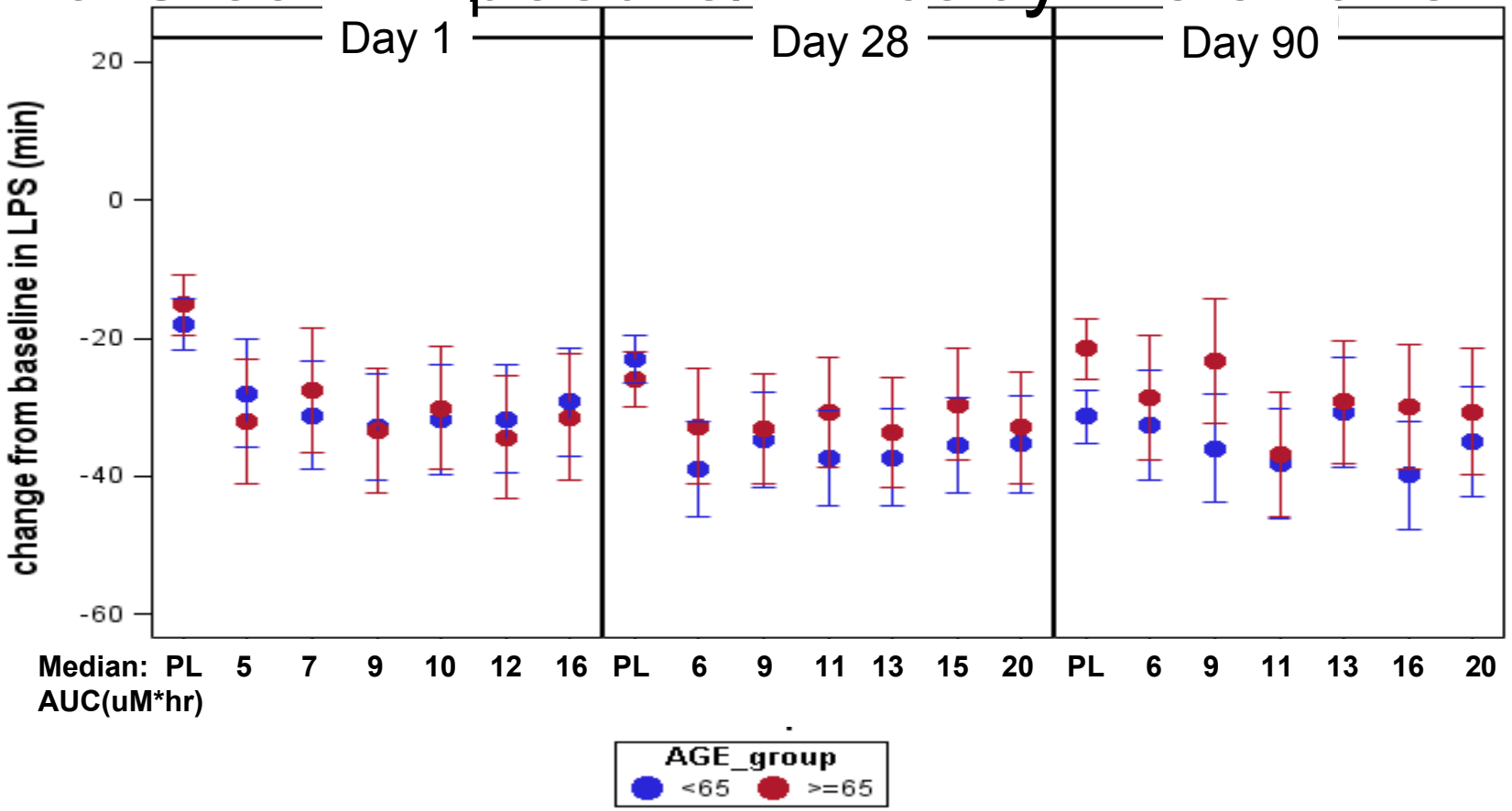
Sleep Maintenance
No Clear Exposure/Efficacy Relationship



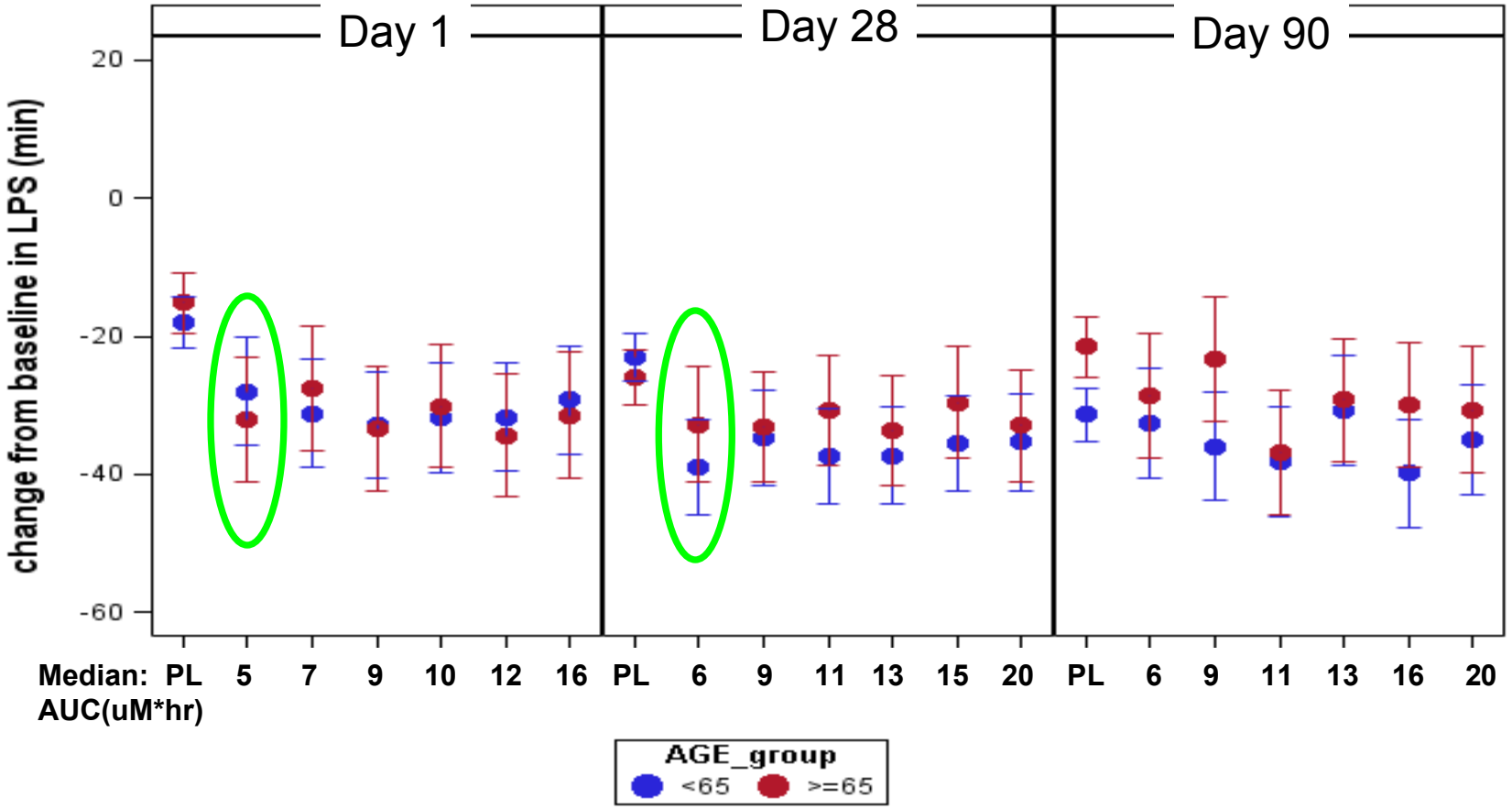
Sleep Maintenance
Exposure Similar to 10 mg is Effective



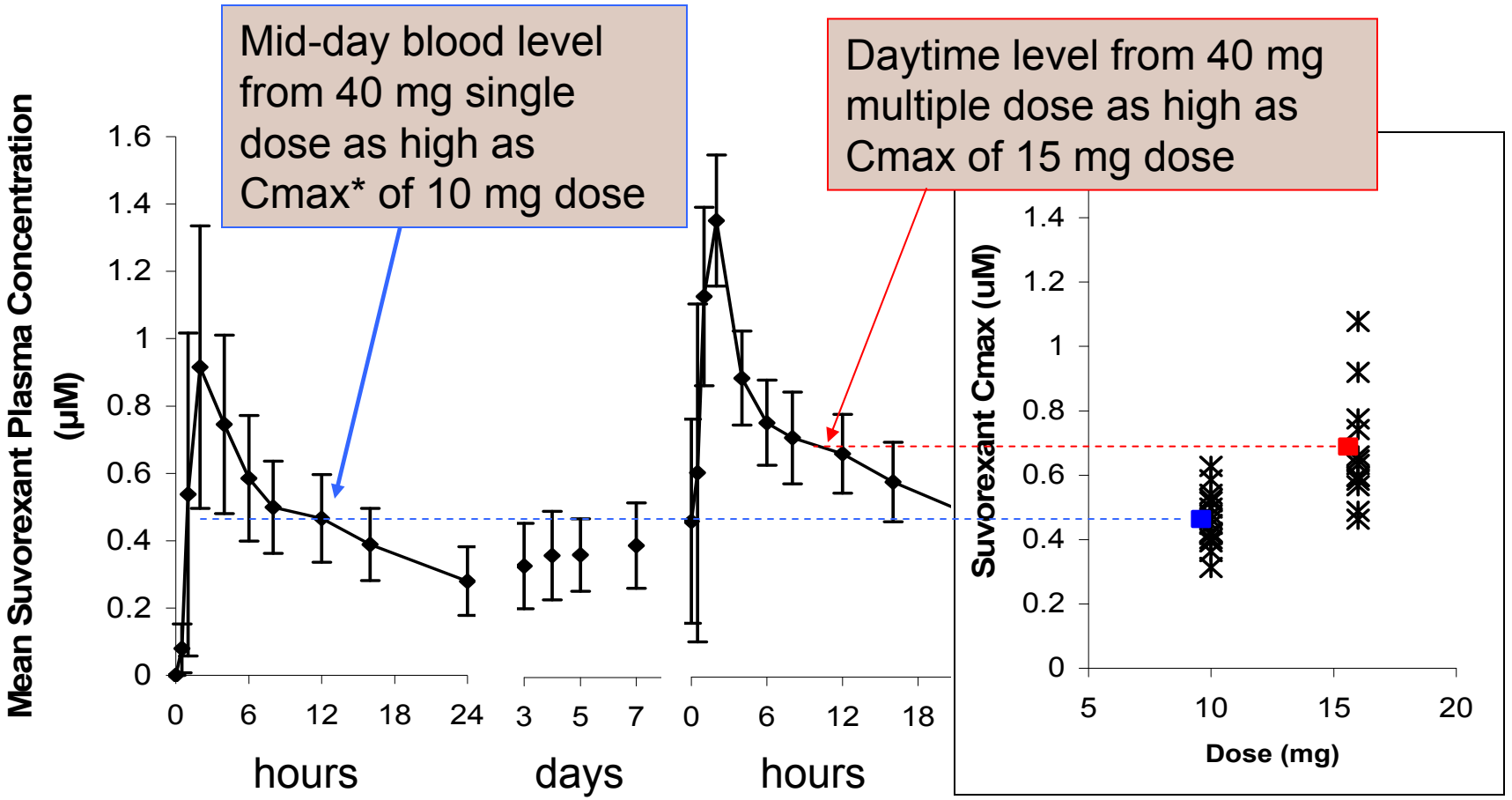
Sleep Onset
No Clear Exposure/Efficacy Relationship



Sleep Onset
Exposure Similar to 10 mg is Effective



12-hour half-life: ***High levels during day; levels accumulate***



*Cmax: maximum concentration

Healthy Subjects (N=19)

Pharmacokinetics and Efficacy

- Efficacy for sleep latency expected to depend on delay between dosing and drug reaching effective level in blood/brain

- Time to reach maximum blood levels (Tmax) of suvorexant ≈ 1 to 2 hours if fasted, ≈ 3 hours if fed

Pharmacokinetics and Efficacy

- Some evidence suggests dose-response for sleep latency on night 1
  - because of 12-hour half-life, with daily use blood levels present *before* dosing likely contribute to efficacy for sleep latency
- May be worthwhile to explore strategies to maximize efficacy of 10 mg or lower doses
  - Is it safe to dose earlier than at time in bed?

Smaller Dosage Form than 15 mg May be Necessary

> 1.5-fold mean exposure increase in obese patients relative to patients with normal weight

≈ **2 to 3** fold higher exposure in obese women vs. non-obese men

May be a third of target clinical population

Also, patients taking drugs that inhibit suvorexant metabolism, taking other sedating drugs, or patients simply at the high end of the population distribution of blood levels or pharmacodynamic sensitivity

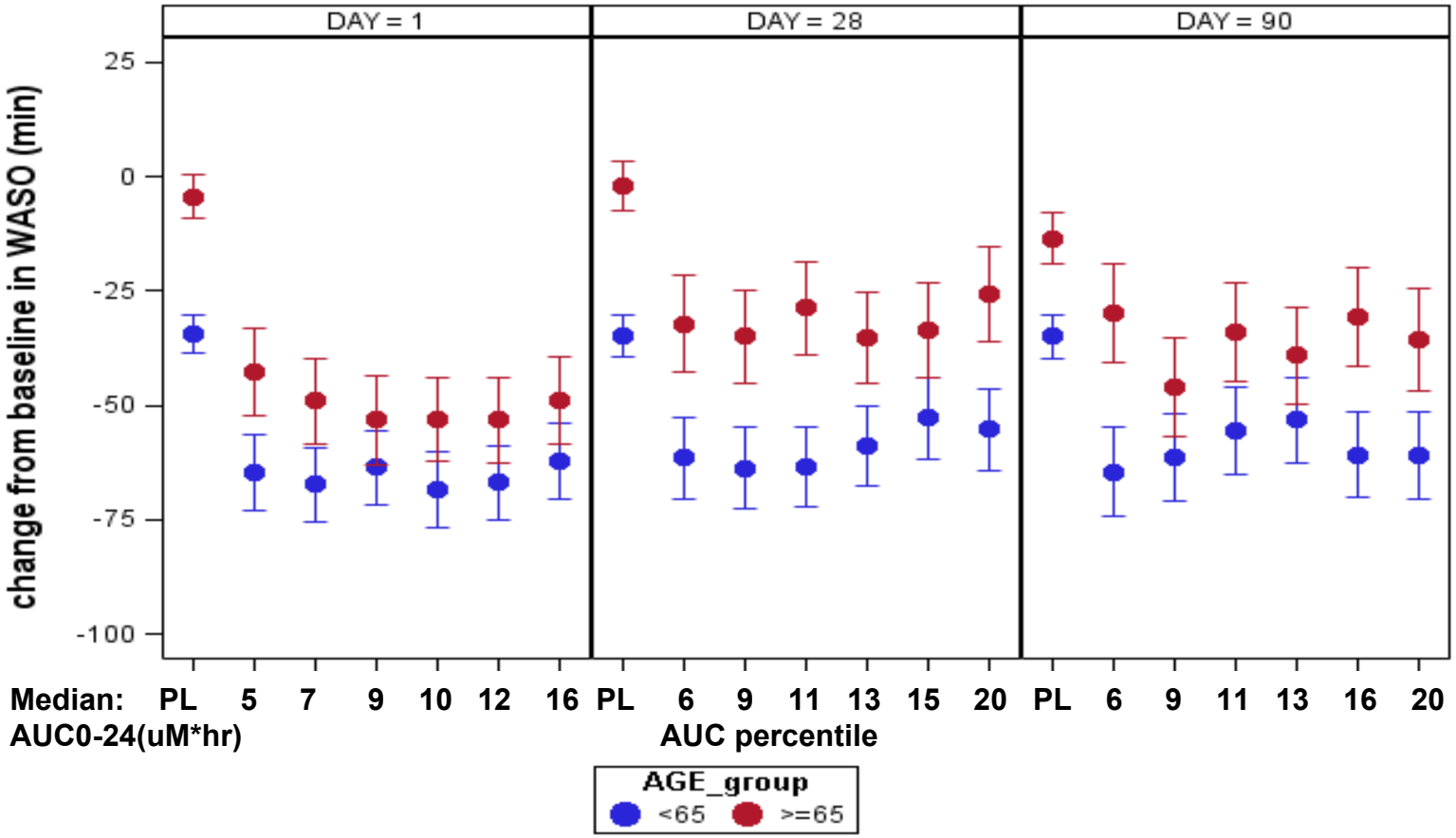
Adult vs Elderly

- Dose adjustment may not be necessary based on age alone
- Elderly blood levels 15% higher than adult…
- But no evidence that elderly more sensitive
  - Safety
    - next day somnolence AE's *less* in elderly
    - *30 mg* elderly driving impairment similar to *20 mg* adult
  - Efficacy
    - similar exposure-response relationship

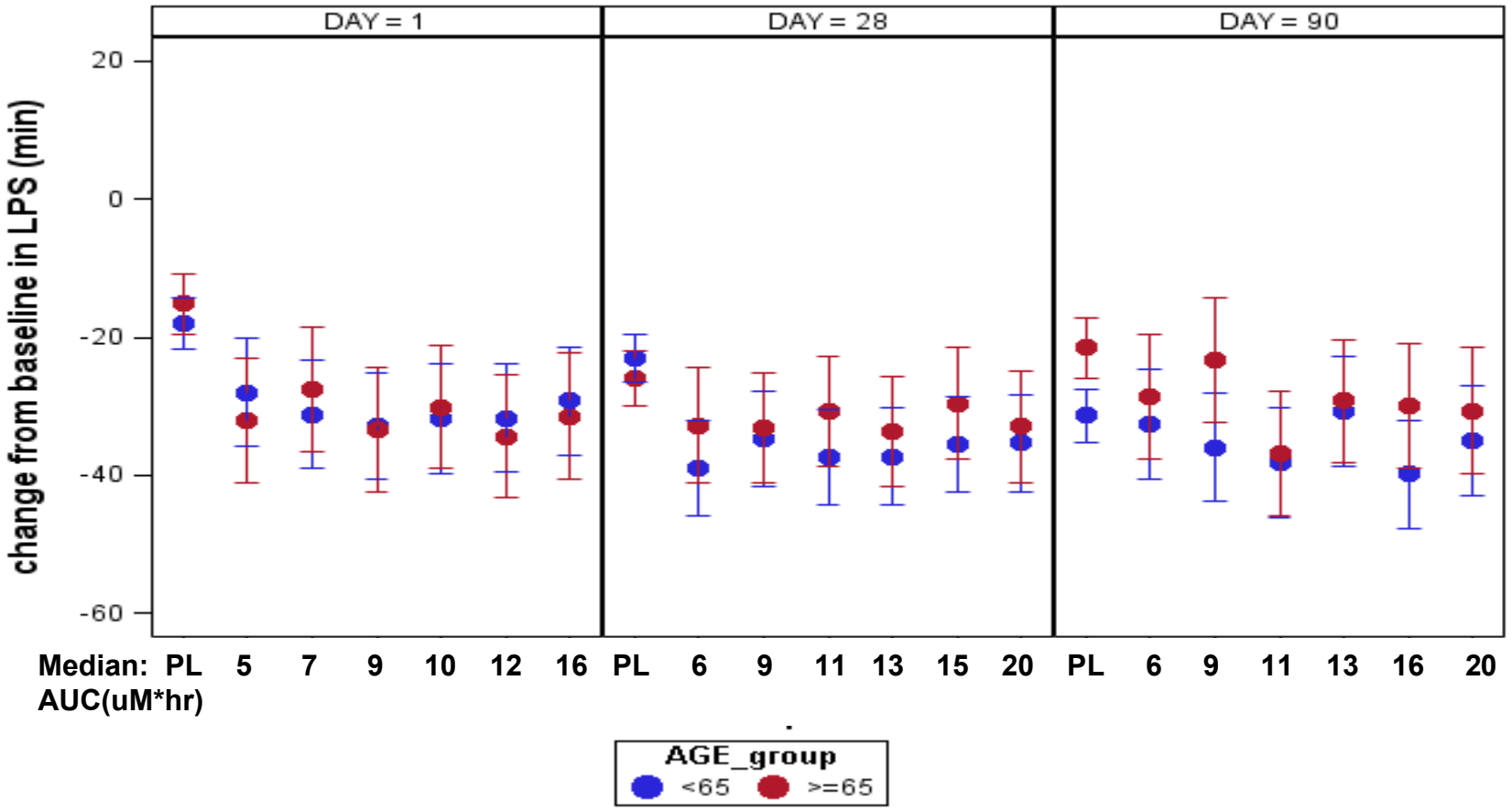
- Elderly: 30 mg somnolence ≈ 20 mg adult
- Women: 25-30% higher exposure than men
  -more somnolent than men at same dose

	Placebo (N=1025)	**Low Dose (N=493)**	**High Dose (N=1291)**
>=65 y	**3%**	**5%**	**9%**
<65 y *higher dose*	**3%**	**8%**	**13%**
F *higher exposure*	**2%**	**9%**	**11%**
M	**4%**	**3%**	**10%**

Sleep Maintenance
Similar Exposure/Response *Adult* & *Elderly*



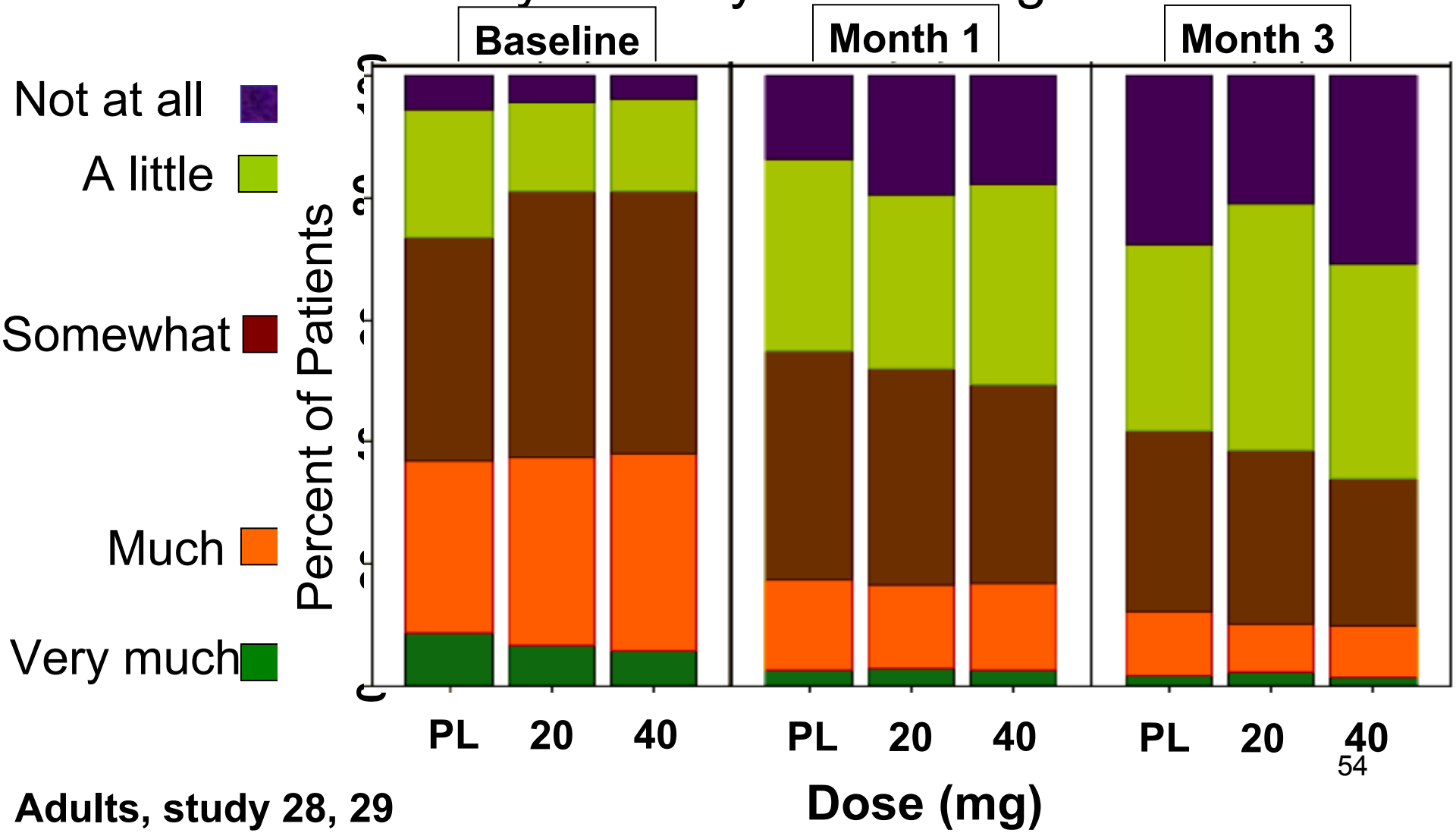
Sleep Onset
Similar Exposure/Efficacy *Adult* & *Elderly*



Benefit/Risk

- Increased FDA focus on patient perspective on disease severity in benefit/risk assessment
- We know from subjective sleep endpoints that patients find suvorexant increases time slept…
- But subjective *daytime function* seems a key measure not otherwise captured
  - Benefit seems modest; much larger effect of *time*
  - For the most severely affected patients, little difference between drug and placebo

To what extent do you consider your sleep problem to INTERFERE with your daily functioning CURRENTLY?



Adults, study 28, 29

Conclusions

- Major safety concerns
  - Daytime somnolence
  - Impaired driving
  - Unconscious nighttime behaviors
  - Suicidal ideation
  - Narcolepsy-like syndrome

Conclusions

- 30 mg and 40 mg seem unsafe
- 20 mg impairs driving in adults
- 15 mg in obese women and patients taking moderate CYP3A4 inhibitors leads to average exposures similar to those from *30* mg
- Counting obese men, pre-obese women, concomitant drug use, etc, 15 mg may be too high for *majority* of target patients

Conclusions

- Potentially serious adverse effects clearly dose-related
- Patients can't reliably respond to their own risk from drug
- No clear efficacy decrease down to, and including, 10 mg
- Risk/benefit balance might be better even *if* less than maximum efficacy at doses lower than 10 mg
- No apparent justification for using higher doses of insomnia drug than necessary for efficacy

Conclusions

- Risk of adverse effects might be higher in general insomnia population
- Even small absolute increase in risk for common events may be highly relevant
  - 38,364 suicides in US in 2010*
  - 33,687 deaths from motor vehicle accidents*
- Effort to find the lowest effective dose may be warranted

*CDC Morbidity and Mortality Weekly Report, http://www.cdc.gov/mmwr